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Broader, Greener, and More Efficient: Recent Advances in Asymmetric Transfer Hydrogenation

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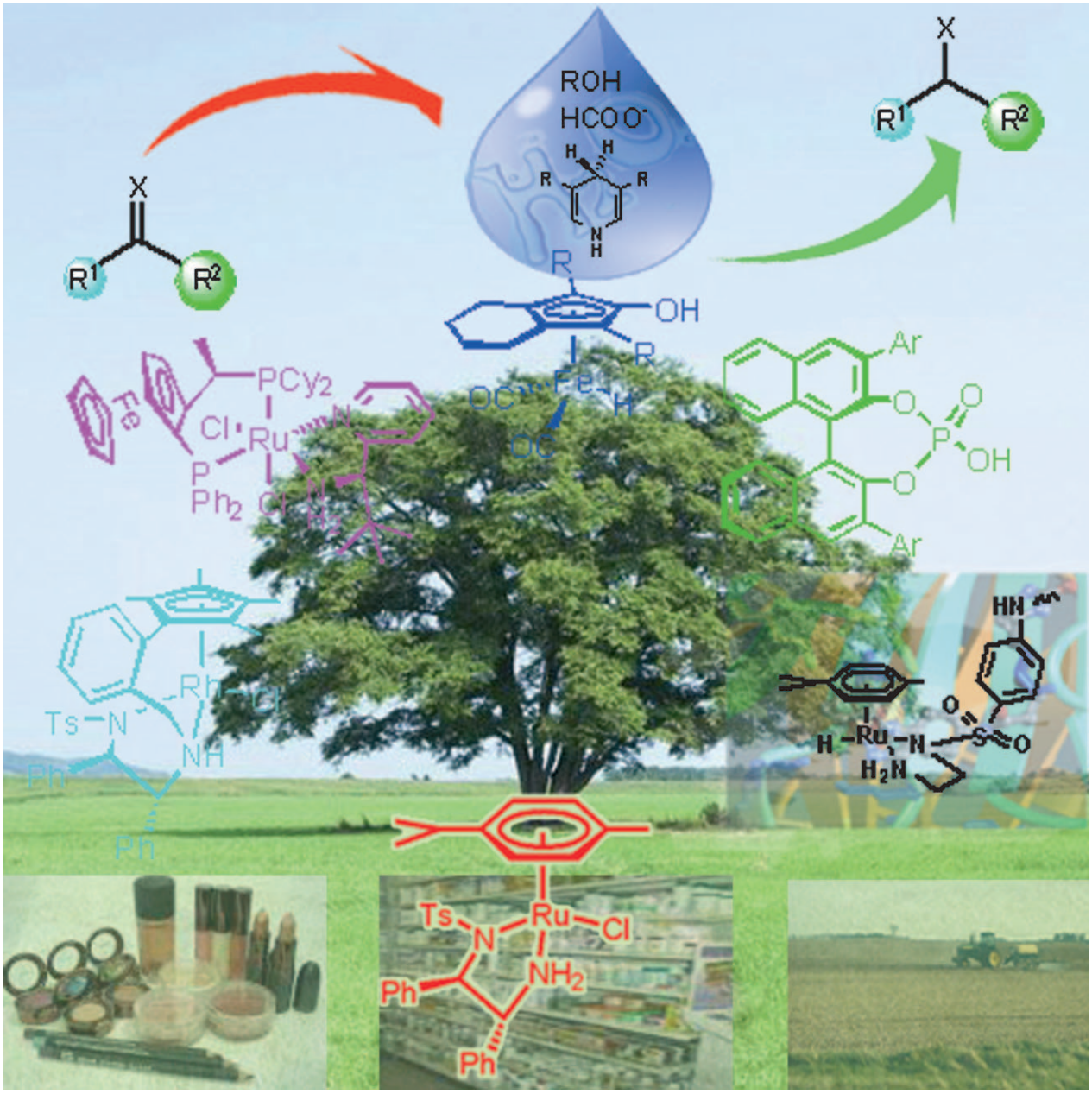
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday



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Abstract: Asymmetric transfer hydrogenation has become a practically useful tool in reduction chemistry in the last decade or so. This was largely triggered by the seminal work of Noyori and co-workers in the mid-1990s and is driven by its complementing chemistry to hydrogenation employing H_2. This Focus Review attempts to present a "holistic" overview on the advances in the area, focusing on the achievements recorded around the last three years. These include more-efficient and "greener" metal catalysts, catalysts that enable hydrogenation as well as transfer hydrogenation, biomimetic and organocatalysts, and their applications in the reduction of C=O, C=N, and C=C bonds. Also highlighted are efforts in the development of environmentally benign and reusable catalytic systems.

Keywords: asymmetric catalysis · green chemistry · homogenous catalysis · hydrogenation · organocatalysis

1. Introduction

The reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst is known as asymmetric transfer hydrogenation (ATH). Because of its operational simplicity and versatility, ATH has become one of the best reduction systems for both academia and industry.

Although enzymes are well known to be highly enantioselective in ATH by using NADH or NADPH as a hydrogen donor, it took chemists several decades to develop chemical catalysts with selectivities approaching those of enzymes. The first ATH was reported by Doering and Young, who designed an asymmetric version of the Meerwein–Pondorf–Verley reduction of ketones by using an achiral catalyst and a chiral hydrogen source.[1] In the 1970s, the Ohkubo and Sinou groups demonstrated the feasibility of using a chiral transition-metal catalyst to achieve ATH by combining $[RuCl_2(PPh_3)_3]$ with a chiral monophosphine ligand.[2] Since then, several chiral catalytic systems for ATH have been developed, including Pfaltz's iridium,[3] Genet's ruthenium,[4] Lemaire's rhodium,[5] and Evans' samarium systems.[6] However, there were few transition-metal catalysts that could provide enantioselectivity exceeding 90% *ee* before 1995. A significant breakthrough in transition-metal-catalyzed ATH was then made by Noyori and co-workers; Ru^{II} catalysts bearing monotosylated 1,2-diamines or amino alcohols were discovered to be highly efficient and enantioselective for the reduction of ketones with isopropyl alcohol (IPA) or $HCOOH/Et_3N$ azeotrope.[7]

These Noyori–Ikariya-type catalysts, which have found broad applications[8] and operate through a novel metal–ligand bifunctional mechanism,[9] have since inspired intense research into ATH. The concept of bifunctional catalysis has also been extended into the design of catalysts for other chemical transformations,[10] and efforts have been made to immobilize the catalysts and develop more environmentally benign reaction conditions. New catalysts, which are more efficient or more economic and "greener", are being searched. Alongside the organometallic catalysts, biomimetic and organocatalytic ATH has emerged, providing new tools for organic synthesis and insight into processes in nature. The remarkable progress in ATH, including mechanistic understanding, that has been made in the past one decade or so, has been extensively reviewed.[8c,9e,11] Hence, in this Focus Review, we place emphasis on more recent advances, particularly those dealing with new catalytic systems reported around the last three years.

2. More-Selective, Faster, and Greener Catalysts

Ever since Noyori and co-workers disclosed the metal–ligand bifunctional Ru^{II} catalysts, many new catalysts have been discovered or designed for ketone reduction. These include those ligated with bidentate ligands, such as diamines,[12] amino alcohols,[13] tridentate ligands,[14] and tetradentate ligands,[15] most of which are capable of metal–ligand bifunctional cooperation. Some representative ligands are shown in Scheme 1, and their applications in ATH have been summarized before.[8c,11]

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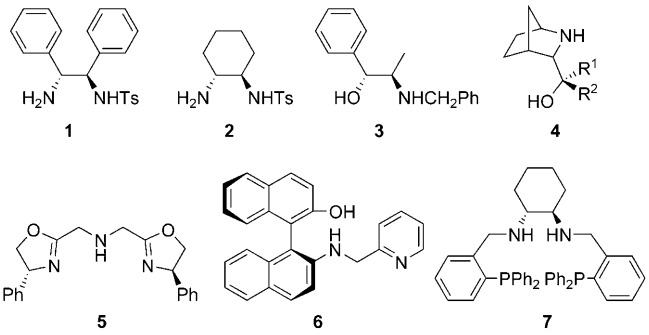
Among the emerging catalysts, the structurally rigid, tethered ruthenium and rhodium catalysts developed by Wills and co-workers are of particular note.[16] The tether offers an additional element in controlling enantioselection and in stabilizing the catalysts. Thus, the Ru^{II} catalysts **8** and **9** are good ATH catalysts, generally providing faster reaction rates than the nontethered analogues for ketone reduction using HCOOH/Et_3N azeotrope as the hydrogen donor (Scheme 2).[16a–c,f] The Rh^{III} catalyst **10** affords a remarkably high enantioselectivity of 99.9% *ee* for tetralone reduction and is particularly good for the ATH of α-substituted aromatic ketones.[16d] Of still further interest is the Rh^{III} catalyst **11**, which represents one of the best ATH systems for aliphatic ketone reduction, providing an *ee* value of 87% in the reduction of cyclohexylmethyl ketone using HCOOH/Et_3N azeotrope as the hydrogen donor (Scheme 2).[16e] These catalysts are also active in water without compromising enantioselectivity (see below).

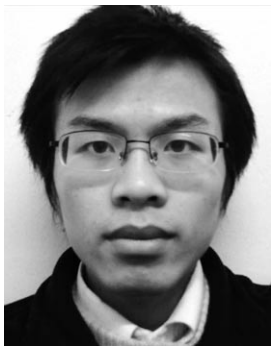


Scheme 1. Representative ATH ligands.

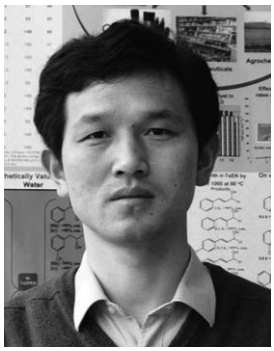
Adolfsson and co-workers found that amino acid derivatives can act as ligands in ATH reactions.[17] By simply changing the functionality on the same amino acid backbone, the Rh^{III} catalysts were shown to be enantioswitchable. For instance, the ligand **13** and **14** both gave the *R*-configured product in the reduction of acetophenone, indicating that the stereocenter in the amino acid backbone dictates the facial selection of ketone; having the same amino acid backbone, however, ligand **12** produced the *S* product (Scheme 3).[17f,g] Although the reason behind this result is still not clear, this enantioswitchable feature allows access to both enantiomers.

Two other types of catalyst are worth noting. Cyclometalated ruthenium complexes generated from $[Ru(\eta^6\text{-arene})Cl_2]_2$ and simple chiral amines proved to be active catalysts for ketone reduction by de Vries and co-workers, affording up to 89% *ee*.[18] Reetz and co-workers reported that the Ru^{II} catalysts, which unusually contain a phosphite ligand **15**, could produce high enantioselectivities for both aromatic and aliphatic ketones (Scheme 4).[19] Aliphatic ketones, challenging substrates for normal ATH catalysts, were reduced with up to 99% *ee* using IPA as the hydrogen donor.

Highly active and productive transfer hydrogenation catalysts are emerging, with TOFs and TONs comparable to some of the best asymmetric hydrogenation catalysts. Baratta and co-workers have developed a series of very active ruthenium catalysts for the transfer hydrogenation of ketones.[20] The cyclometalated Ru^{II} complex **16** was initially shown to be a highly active transfer hydrogenation catalyst, affording TOFs up to $6\times10^4\ h^{-1}$ in the reduction of acetophenone using IPA as the hydrogen source in the presence of a base (Scheme 5).[20a] Further development led to the Ru^{II} complex **17** bearing a CNN ligand[20b] and the Ru^{II} complex **18** bearing a cyclometalated carbene,[20c] both of which



Chao Wang *was born in Hunan, China in 1981. He received his BSc in Chemistry from Hunan Normal University in 2004. He then moved on for an MSc in Organic Chemistry with Prof. Yi Jiang at the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences. Since 2007, he has been a PhD student in Prof. Xiao's group at the University of Liverpool. His current research interests lie in the field of catalysis, organic synthesis, and organometallic chemistry.*



Xiaofeng Wu *graduated from the East China University of Science and Technology (ECUST, Shanghai) with a BSc in applied chemistry in 1995, and became Lecturer at the same university in 1999. He did his MSc in organic chemistry at the Shanghai Institute of Organic Chemistry (SIOC) under the joint direction of Prof. G. B. Rong of ECUST and Prof. M. Shi of SIOC during 1999–2002. He was then awarded a Fuji Otsuka Fund Research Fellowship to work in the group of Prof. K. Shishido at the University of Tokushima, Japan. From 2004 to 2007, he worked on his PhD with Prof. Xiao at the University of Liverpool, focusing on the chemistry of asymmetric transfer hydrogenation in water, and has since been a postdoctoral research fellow. His scientific interests include organic synthesis, organometallics, catalysis, and green chemistry.*

Jianliang Xiao *received his BSc in chemical engineering at the Northwest University in 1982. This was followed by an MSc in catalytic engineering with Profs. Chi Wu and JunYu Wang at the Research Institute of Petroleum Processing in Beijing. To support his interest in heterogeneous catalysis, he went to the University of Alberta for a PhD in organometallic chemistry under Prof. Martin Cowie. After a two-year postdoctoral appointment with Prof. Richard Puddephatt, he joined the ERATO Molecular Catalyst Project as a Researcher under the direction of Prof. Ryoji Noyori. In 1996, he took up a Principal Scientist position at the Leverhulme Centre for Innovative Catalysis at the University of Liverpool. He was appointed to a Lectureship in the Chemistry Department in 1999, and then promoted to Reader and more recently full Professor in early 2005. He is now Professor of Catalysis.*

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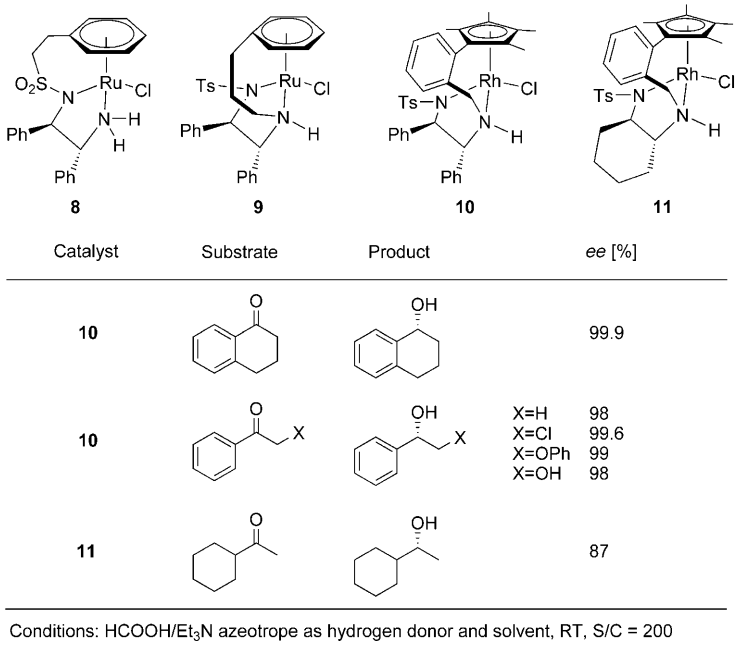
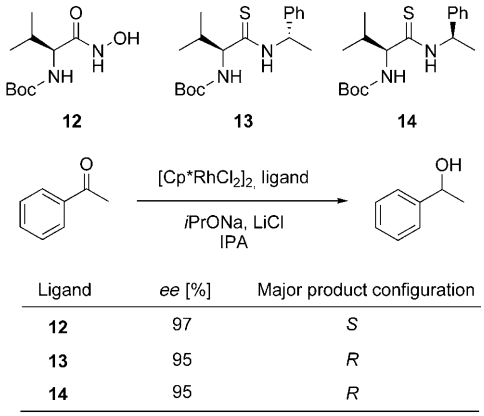


Scheme 2. Tethered catalysts and their applications in ATH.

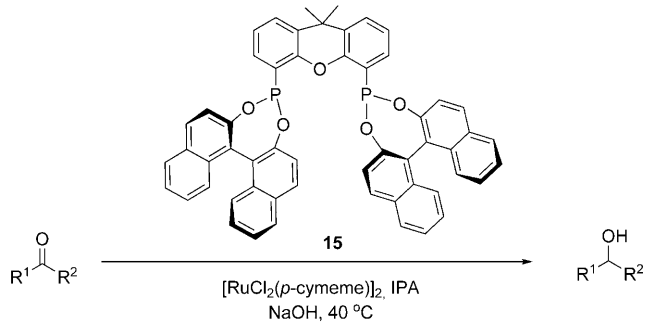


Scheme 3. Enantioswitchable amino acid ligands and their applications.

are excellent transfer hydrogenation catalysts, achieving a TOF of 1.1×10^6 and 1.1×10^5 h^{-1}, respectively, for the reduction of acetophenone.

Asymmetric induction has been demonstrated with similar catalysts. When a chiral CNN ligand was used (**19**), good enantioselectivity was obtained with the high activity retained.[20d] Recently, the Ru^{II} complex **20**, which bears a chiral phosphine ligand and 2-(aminomethyl)pyridine (ampy), was revealed to catalyze the ATH of ketones in IPA, affording up to 3×10^5 h^{-1} TOF and 94% *ee*.[20e] The Ru^{II} complex **21**, obtained in high diastereoselectivity even when racemic 1-(pyridin-2-yl)methanamine (pyme) and a chiral phosphine ligand were used, afforded high TOFs (up to 7×10^4 h^{-1}) and enantioselectivities (up to 99% *ee*) for the ATH of ketones.[20f] The analogous osmium complex is also a viable ATH catalyst, affording up to 5×10^5 h^{-1} TOF and 96% *ee*.[20g] The ampy structure in these catalysts seems to play a crucial role, aiding hydride generation and presumably enantioselective hydride transfer to the ketone.

Other highly active achiral transfer hydrogenation catalysts have also been reported. Mathey, Le Floch, and co-workers showed that the cationic Ru^{II} complex **22** could provide a TOF of 1.2×10^6 h^{-1} in the transfer hydrogenation of acetophenone using IPA as the hydrogen donor.[21] Stradiotto and co-workers reported a novel, formally zwitterionic Ru^{II} complex **23**, which afforded TOFs as high as 2.2×10^5 h^{-1} in ketone reduction in IPA.[22] It is worth noting that catalysts **22** and **23** could not provide a metal–ligand bifunctionality as the Noyori-type ATH catalysts do, suggesting that fast transfer hydrogenation is feasible with other mechanistic pathways. Very recently, Grützmacher and co-workers disclosed a Rh^{I} amido complex **24**, which is capable of transfer hydrogenating ketones and C=C double bonds using ethanol as the hydrogen donor. This is a very efficient catalyst, reducing acetophenone with a TOF up to 6×10^5 h^{-1} with a clean and cheap alcohol as the hydrogen source at 40 °C.[23] Table 1 compares the results obtained with the catalysts **16**–**24** in the transfer hydrogenation of acetophenone. Although



R^1	R^2	Conversion [%]	*ee* [%]
Ph	CH_3	93	98
o-ClC_6H_4	CH_3	90	99
c-C_6H_{11}	CH_3	97	99
$CH(CH_3)_2$	CH_3	99	99

Scheme 4. Ru^{II}-phosphite catalyst for the ATH of aromatic and aliphatic ketones.

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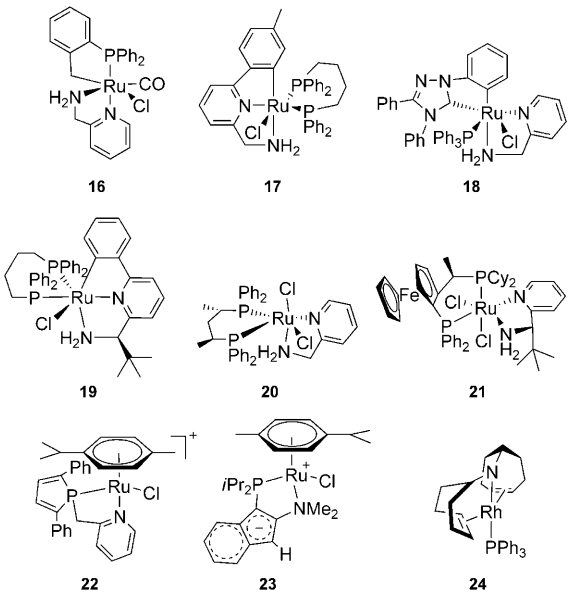
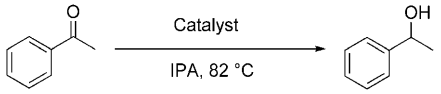


Scheme 5. Highly active catalysts for transfer hydrogenation including ATH.

the asymmetric version of some of these catalysts is not yet available, the discoveries may shed light on the design of new, more effective ATH catalysts.

Parallel to the quest for more-efficient ATH catalysts, the discovery of "greener" catalysts becomes another focal point. Iron, the active site of hydrogenases,[24] is cheaper and more abundant and environmentally benign compared to the more commonly used ruthenium, rhodium, and iridium. However, the development of iron catalysts for hydrogenation or transfer hydrogenation lags far behind. Early in 1972, Noyori and co-workers reported that $[Fe(CO)_5]$ could catalyze the selective hydrogenation of the C=C double bond of α,β-unsaturated ketones and aldehydes.[25] The iron carbonyl was also shown by Marko and co-workers to be a good catalyst for the hydrogenation of imines.[26] Subsequent work from Vancheesan and co-workers demonstrated that iron carbonyls derived from $[Fe_3(CO)_{12}]$ catalyze the transfer hydrogenation of ketones with IPA or 1-phenylethanol as the hydrogen donor, affording moderate to good yields.[27] Later, Bianchini, Graziani, and co-workers reported a nonclassical trihydride **25** to be an effective catalyst for the selective reduction of unsaturated carbonyl compounds, using either IPA or cyclopentanol as the hydrogen donor (Scheme 6).[28] The selectivity between the carbonyl group and C=C double bond was substrate dependent.

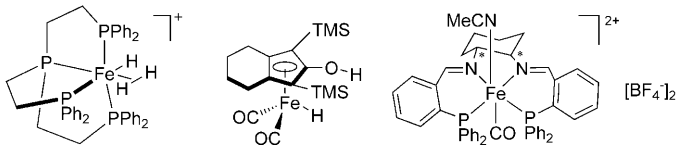
Table 1. Comparison of catalyst performance in the transfer hydrogenation of acetophenone.



Entry	Catalysts	S/C	TOF [h^{-1}]	*ee* [%]	Ref.
1	**16**	2×10^3	6×10^4	–	[20a]
2	**17**	2×10^4	1.1×10^6	–	[20b]
3	**18**	2×10^3	1.1×10^5	–	[20c]
4	**19**	2×10^4	9.3×10^5	71	[20d]
5	**20**	2×10^3	3×10^5	85	[20e]
6	**21**	2×10^3	7×10^4	95	[20f]
7[a]	**22**	2×10^5	1.2×10^6	–	[21]
8	**23**	2×10^3	1.8×10^5	–	[22]
9[b]	**24**	1×10^5	6×10^5	–	[23]

[a] The temperature was 90 °C. [b] Ethanol was used as the hydrogen donor at 40 °C.

Significant progress in transfer hydrogenation with iron catalysts has only been made in the past few years. Beller and co-workers reported iron-terpyridine-phosphine[29] and iron-porphyrin[30] systems for the transfer hydrogenation of ketones using IPA as the hydrogen donor. The easily accessible $[Fe_3(CO)_{12}]$ and $FeCl_2$ were found to be suitable metal precursor in these catalytic systems. Both aromatic and aliphatic ketones were reduced with excellent yields. Casey and co-workers disclosed a bifunctional iron complex **26**, which was capable of both hydrogenation and transfer hydrogenation,[31] presenting the first example of iron catalysts for hydrogenation as well as transfer hydrogenation. High selectivity towards polar multiple bonds, such as carbonyl and imine groups, was observed. Bearing a hydride and an acidic hydrogen atom, the structurally well-defined catalyst



Catalyst	S/C	Hydrogen donor	Temperature [°C]	Time [h]	Yield [%]	*ee* [%]	Ref.
$[Fe_3(CO)_{12}]$/terpy/PPh_3	200	IPA	100	7	95	-	[29]
$[Fe_3(CO)_{12}]$/porphyrin	200	IPA	100	7	94	-	[30]
26	100	IPA	75	16	87	-	[31]
26	50	H_2	25	20	83	-	[31]
$[Et_3NH]^+[HFe_3(CO)_{11}]^-$/**7**	100	IPA	82	7	92	56	[33]
27	200	IPA	22	0.4	95	29	[34]

Scheme 6. Hydrogenation with iron catalysts.

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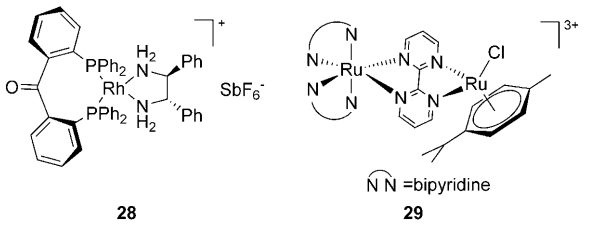
is analogous to the active Shvo ruthenium catalyst[9e,32] and has features reminiscent of diiron hydrogenases.[24]

The first iron catalyst for the ATH reaction was reported in 2004 by Gao and co-workers, who demonstrated that the $[Et_3NH]^+[HFe_3(CO)_{11}]^-$ complex together with the ligand **7**, originally developed by the same group, could catalyze the ATH of ketones in IPA, affording good yields and *ee* values.[33] Very recently, Morris and co-workers reported a structurally well-defined iron ATH catalyst **27**, which afforded up to 907 h^{-1} TOF for ketone reduction, although the enantioselectivity still needs to be improved.[34] The performance of some of the iron catalysts is shown in Scheme 6.

Some new strategies in asymmetric catalysis have also been adopted in ATH. For instance, Mikami and co-workers reported that an achiral ligand could be activated by a chiral ligand when both are coordinated to a metal (Scheme 7).[35]



28 **29**

Scheme 7. Catalysts adopting new strategies.

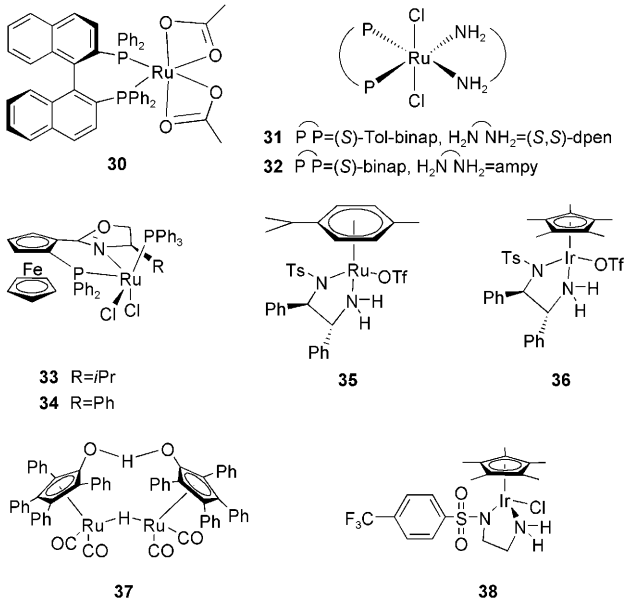
The Rh^I complex **28**, bearing a chirally activated achiral 2,2′-bis(diphenylphosphino)benzophenone ligand, gave virtually perfect enantiocontrol in the ATH of ketones, outperforming its enantiopure binap counterpart. In the reduction of 2-methyl acetophenone, complex **28** afforded a 99% *ee* value while the binap complex only gave a 57% *ee*. As aforementioned, the highly active ATH catalysts **21** reported by Baratta and co-workers incorporate a somewhat similar tactic.[20f,g]

Hamelin and co-workers synthesized the complex **29** from an octahedral, "chiral-at-metal" complex Λ-$[Ru(bipyridine)_2(bipyrimidine)]^{2+}$, without using any chiral ligands. In the ATH of ketones, **29** afforded *ee* values of up to 26%, with the chiral information being relayed through the bridging bipyrimidine ligand.[36] Although the enantioselectivity is low, this "chiral inorganic ligand" may lead to the design of new catalysts.

3. Towards "Universal" Catalysts

Discovery of "universal" catalysts, which are not only efficient for asymmetric hydrogenation (AH) but also for ATH, is a long-term objective for chemists. Catalysts of this type are intellectually appealing and would be practically more useful. In general, however, catalysts that are efficient for hydrogenation tend to be poor for transfer hydrogenation, and vice versa. The main reason might be, as Ikariya pointed out in 2001, that the electronic properties on the metal center are vital to determine whether a catalyst is suitable for hydrogenation or for transfer hydrogenation.[37] We must also note that the mode of hydride generation is fundamentally different in hydrogenation with H_2 versus transfer hydrogenation with, for example, IPA.

For almost all the functional groups, hydrogenation has been more successful than transfer hydrogenation. In the 1990s, some good hydrogenation catalysts were tested for transfer hydrogenation reactions, but only a few exhibited good performance in transfer hydrogenation in terms of catalytic activity and enantioselectivity. An earlier example is seen in the Ru^{II}-binap complex **30** (Scheme 8), which was



30 **35** **36** **37** **38**

Scheme 8. Catalysts capable of both hydrogenation and transfer hydrogenation.

first employed by Noyori and co-workers in the AH of α,β-unsaturated carboxylic acids, demonstrating excellent stereocontrol for various substrates.[38] This catalyst was investigated by Brown and co-workers in the ATH of α,β-unsaturated carboxylic acids using HCOOH/Et_3N azeotrope as the hydrogen donor, affording moderate enantioselectivities.[39] Later Saburi and co-workers found that simple alcohols, such as IPA or ethanol, are good hydrogen donors for the ATH of α,β-unsaturated carboxylic acids using a similar complex.[40] The catalyst was also tested by Genet, Khai, and their co-workers in the ATH of ketones using IPA or $[Et_3NH]^+[H_2PO_2]^-$ as the hydrogen donor.[4,41] These catalysts showed better enantioselectivities in hydrogenation than in ATH, however.

The Ru^{II}-diamine-diphosphine complex **31**, one of the best AH catalysts for ketones developed by Noyori and coworkers,[42] was studied by Morris and co-workers for ATH; but both the activity and enantioselectivity were poor under ATH conditions.[43] Thus, while S/C ratios of up to 2×10^6 and high *ee* values (up to 99%) were demonstrated for a va-

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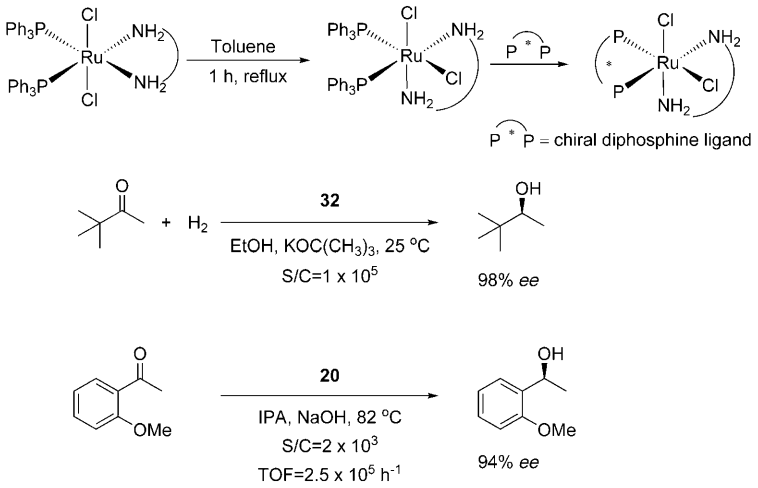


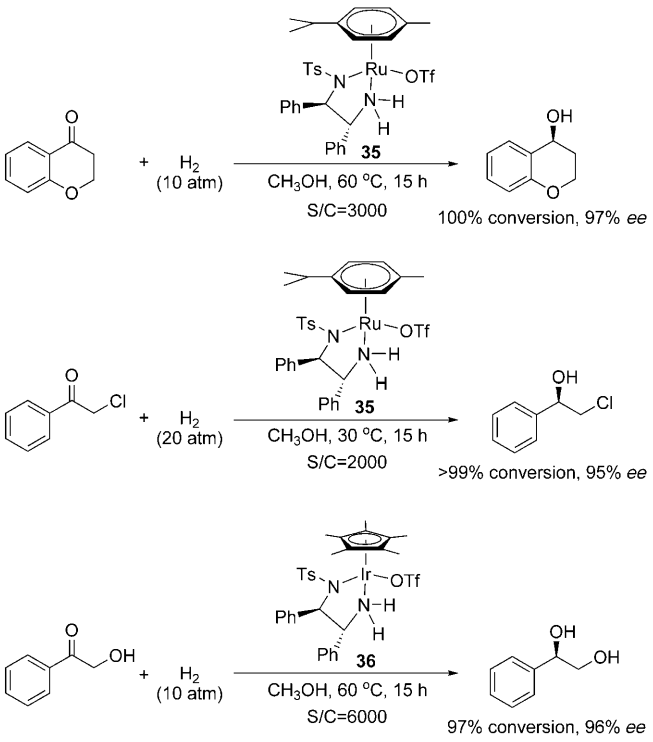
Scheme 9. Hydrogenation and transfer hydrogenation with structurally similar catalysts.

riety of substrates in hydrogenation, the system showed much lower catalytic activity and enantioselectivity in ATH.

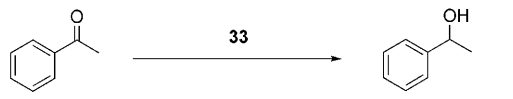
In 2005, Noyori and co-workers found that by using ampy instead of symmetric diamine in the Ru^{II}-diphosphine-diamine system, alkyl ketones could be reduced with high efficiency and enantioselectivity via AH by **32** (Scheme 8).[44] In a related study, Baratta and co-workers observed that the *trans*-$[RuCl_2(PPh_3)_2$(diamine)] complex could be converted into the *cis* isomer upon refluxing in toluene, which could be further converted into a chiral Ru^{II} complex without altering its configuration (Scheme 9).[20e] This subtle change in configuration and the use of ampy as ligand resulted in highly active transfer hydrogenation catalysts, such as **20** and **21** discussed above (Scheme 9).[20e,f,g] However, it remains to be seen whether this configuration change is necessary for an effective AH–ATH switch.

On the other hand, some ATH catalysts have proved to be good AH catalysts recently. Blaser and co-workers reported that the Ru^{II}-oxazoline complexes **33** and **34** (Scheme 8), successful in ATH reactions,[45] can serve as good AH catalysts.[46] Under hydrogenation conditions, the S/C ratio could be increased to 5×10^4 with a TOF of up to 9800 h^{-1} obtained for acetophenone reduction, and high substrate concentration was tolerated (Scheme 10). The TOF in ATH was much lower, however.

Very recently, Ohkuma, Noyori, and co-workers disclosed that the complex **35**, derived from the now "classic" chloride analogue, which is highly successful in ATH,[7a] could be used to activate dihydrogen in polar solvents.[47] With triflate as the counterion, **35** is more easily ionized, generating a cationic species, which provided excellent activity and enantioselectivity in the hydrogenation of ketones. Base-sensitive substrates, such as 4-chromanone, could be enantioselectively hydrogenated to afford up to 97% *ee* with an S/C ratio of 3000 under 10 atm H_2 pressure (Scheme 11). More recently, Ohkuma and co-workers reported that base-sensitive α-hydroxyl aromatic ketones and α-chloro aromatic ketones could also be reduced using a similar Ir^{III}-tsdpen catalyst **36** or the Ru^{II} complex **35** (Scheme 11).[48]



Scheme 11. ATH catalysts for AH.



Hydrogen donor	Conversion [%]	*ee* [%]	TOF [h^{-1}]	Ref.
IPA	94	>99.6	94	[45d]
H_2	98	98.5	9800	[46]

Scheme 10. Ru^{II}-oxazoline complex for both transfer hydrogenation and hydrogenation.

Mechanistic studies revealed that both the ATH and AH proceed through a metal–ligand bifunctional pathway.[49] However, the cationic species is the key to the success of the hydrogenation, as it enables efficient hydride formation from H_2 (Scheme 12). Recent work from Rauchfuss and coworker supports this view; protonation of a 16e Ir^{III} analogue accelerates the generation of an analogous Ir^{III}-H spe-

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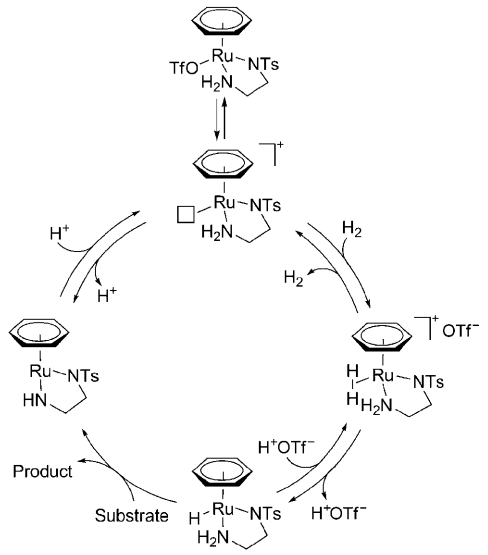


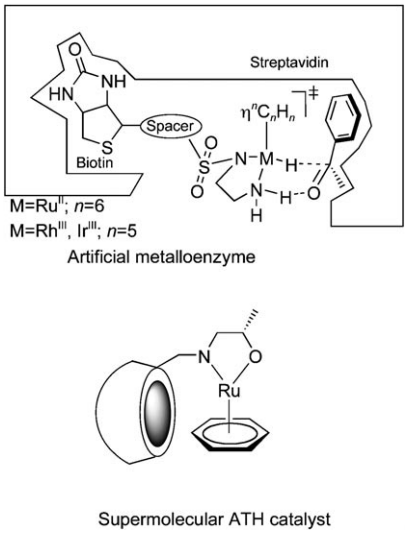
Scheme 12. Catalytic cycle for AH by ATH catalysts.

cies from H_2.[50] In contrast, the Ru^{II}-H hydride in ATH can be readily formed from either the neutral Ru^{II}-Cl precatalyst and formate or the 16e species and an alcohol, such as IPA,[7d,51] highlighting the difference in hydride formation in ATH and AH.

There are also some achiral catalysts which are capable of both hydrogenation and transfer hydrogenation. For instance, the Shvo catalyst **37** (Scheme 8), which was reported to be efficient in hydrogenating various substrates,[32a] was used by Bäckvall and co-workers for the transfer hydrogenation of ketones and imines using IPA as the hydrogen source.[52] The mechanism of the ketone reduction under transfer hydrogenation conditions is shown to be concerted, with the hydroxy group on the arene ligand acting as a proton donor or Lewis acid; however, the mechanism of imine reduction is less clear.[32a,b,53] Very recently, we demonstrated that the Ir^{III}-diamine complex **38** (Scheme 8) is a good catalyst for aldehyde reduction under both transfer hydrogenation and hydrogenation conditions in water, providing a fast reaction rate and excellent chemoselectivity towards the formyl group (see below).[54]

4. Learning from Nature: Biomimetic and Organocatalytic Transfer Hydrogenation

Inspired by nature, much effort has been made to mimic the function of enzymes. In the area of ATH, considerable progress has been witnessed in artificial metalloenzyme design and organocatalysis. Early in 1978, Whitesides and co-workers disclosed that an achiral Rh^{I}-diphosphine complex, bound to a protein through noncovalent interactions, can induce moderate enantioselectivity in the hydrogenation of α-acetamidoacrylic acid.[55] This concept was further studied by Chan and co-workers,[56] and more recently was extensively developed by Ward and co-workers.[57] Biotin displays a strong affinity for strept(avidin), allowing biotinylated molecular metal catalysts to be incorporated into proteins and so giving rise to artificial metalloenzymes. Using biotinylated achiral Ru^{II}-diamine catalysts, Ward and co-workers showed that the resulting artificial metalloenzymes are capable of ATH reactions using HCOONa as the hydrogen source (Scheme 13).[57c,d] Up to 92% conversion and 94% *ee*



Scheme 13. Biomimetic catalysts capable of ATH.

were obtained in the ATH of aryl ketones under optimal conditions. An attractive feature of these metalloenzymes is that they can be optimized or evolved both chemically and generically, thus providing a wide parameter space to discover catalysts of desired capability. Indeed, by saturation mutagenesis of the host protein and chemical modification of the spacer and metal complex, *ee* values of up to 97% were obtained for aromatic ketones.[57e] When armed with structural information and chemogenetic and high-throughput technologies, artificial metalloenzymes of practical potentials could be discovered in a faster and more designed manner.[57f]

The design of catalysts based on a supramolecular architecture is another approach for chemists to mimic nature. Woggon and co-workers reported that Ru^{II} complexes of β-cyclodextrin modified with amino alcohols could serve as efficient ATH catalysts in water using HCOONa as the hydrogen source (Scheme 13).[58] Unconjugated ketones were reduced with high *ee* values and yields, although the S/C ratios were low (Scheme 14). The β-cyclodextrin was considered to play an important role in the enantiocontrol through preorganization of the substrates in its hydrophobic cavity. Very recently, the same group disclosed a related catalyst with the ruthenium unit attached to the secondary face of β-cyclodextrin.[59] The catalyst allows for ATH of the challenging aliphatic ketones, impressively affording *ee* values of up to 98% (Scheme 14). The enantioselection presumably arises from chiral relay from β-cyclodextrin to the ruthenium center, changing the later into a "chiral-at-metal" species.

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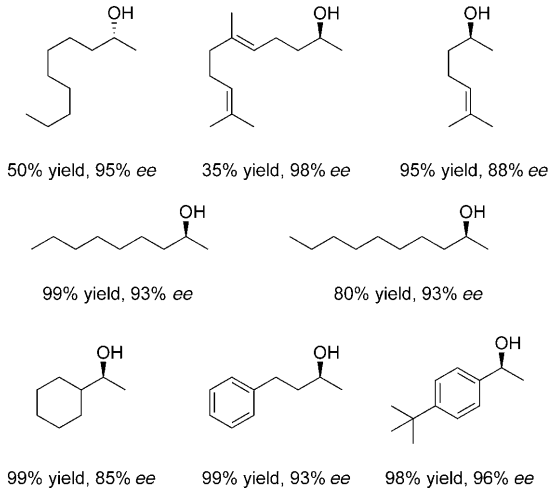
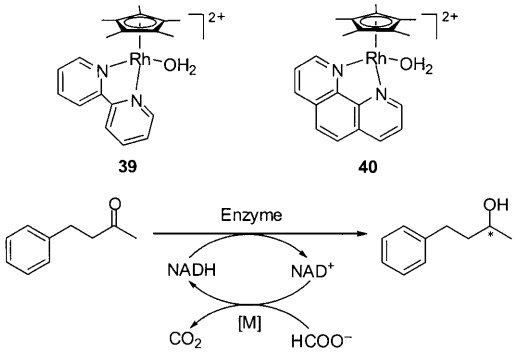


Scheme 14. Products from ATH by β-cyclodextrin-based catalysts.

The regeneration of NADH or NADPH provides impetus for developing enzyme-compatible metal catalysts. Most enzymes involved in redox reactions rely on the cofactors NADH or NADPH to provide hydrogen; these cofactors are expensive to acquire, however. Steckhan and co-workers first reported that the Rh^{III}-bipyridine complex **39** could convert NAD^+ and $NADP^+$ into NADH and NADPH using formate as the hydrogen source (Scheme 15).[60] This regeneration system could be combined with alcohol dehydrogenases to reduce ketones, affording up to 99% *ee*.[61] Recently, Schmid and co-workers also reported that the Rh^{III}-bipyridine catalyst could be coupled with both reduction and oxidation enzymes.[62] Gram-scale production of chiral alcohols has been achieved with this type chemoenzymatic method.



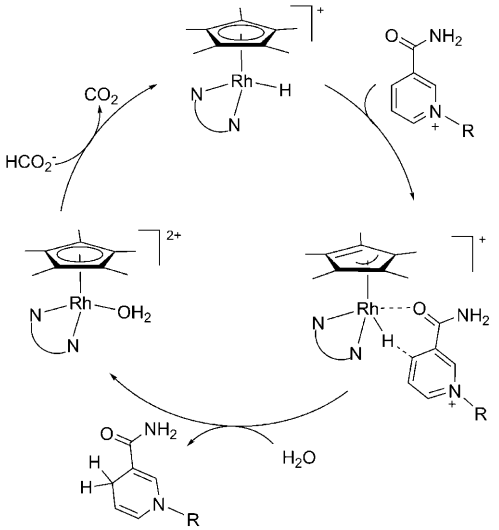
[M]	Enzyme	Hydrogen donor	Time [h]	Conversion [%]	*ee* [%]	Ref.
39	HLADH	HCOONa	24	90	96	[60b]
39	S-ADH	HCOONa	43	89	>99	[60b]
40	HLADH	HCOONa	24	80	96	[63]

HLADH = horse liver alcohol dehydrogenase
S-ADH = rhodococcus sp alcohol dehydrogenase

Scheme 15. Catalysts for regeneration of NADH and their application in enzymatic reduction.

More recently Suss-Fink and co-workers reported that water-soluble phenanthroline complexes of rhodium, iridium, and ruthenium are efficient catalysts for the regeneration of NADH.[63] The Rh^{III} complex **40** is particularly active, providing up to 2000 h^{-1} TOF for the conversion of NAD^+ into NADH using HCOONa as the hydrogen source. The catalyst is also compatible with enzymes; when coupled with an alcohol dehydrogenase, an 80% conversion and 96% *ee* were obtained for 4-phenylbutan-2-one (Scheme 15).

The mechanism of NADH regeneration has been studied by Fish and co-workers. The proposed catalytic cycle is illustrated in Scheme 16. The hydride transfer to the NAD^+ appears to be assisted by the coordination of amide carbonyl group to the metal center, which presumably is made possible by Cp* ring slippage.[64]



Scheme 16. Proposed mechanism for the regeneration of NADH from NAD^+ by a Rh-bipyridine catalyst.

Mimicking what nature does, organocatalysis using NADH analogues as hydrogen donor, for example, Hantzsch ester, has emerged as yet another powerful tool in ATH.[65] In this approach, a chiral organocatalyst is used to interact with or activate a substrate, while the hydride is enantioselectively transferred from the Hantzsch ester to the substrate. There are mainly two classes of organocatalysts in ATH. One involves iminium catalysis for substrates bearing carbonyl groups, and the other exploits Brønsted acids to form tight ion pairs with a substrate, for example, an imine (Scheme 17). However, the essence of the two approaches shown in Scheme 17 is the same, namely electrophilic catalysis or activation of electrophiles, a tactic exquisitely exploited by enzymes.

The iminium catalysis was developed by MacMillan and co-workers.[66] However, the first application of the iminium catalysis in transfer hydrogenation was reported by the List group, who demonstrated that an achiral ammonium salt

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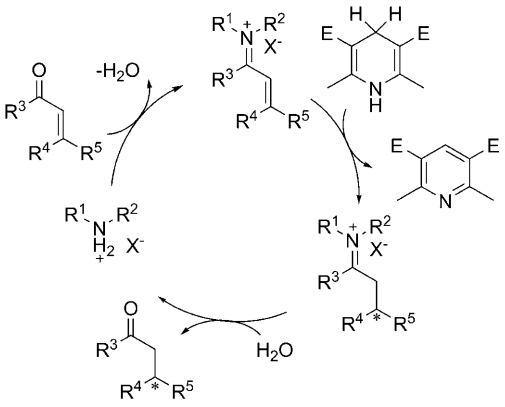
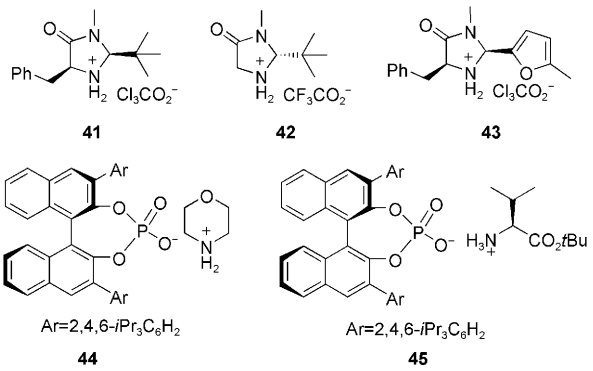
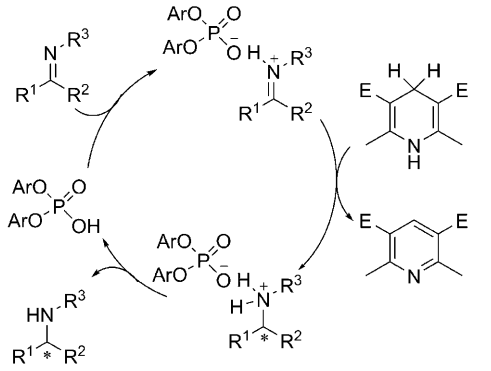




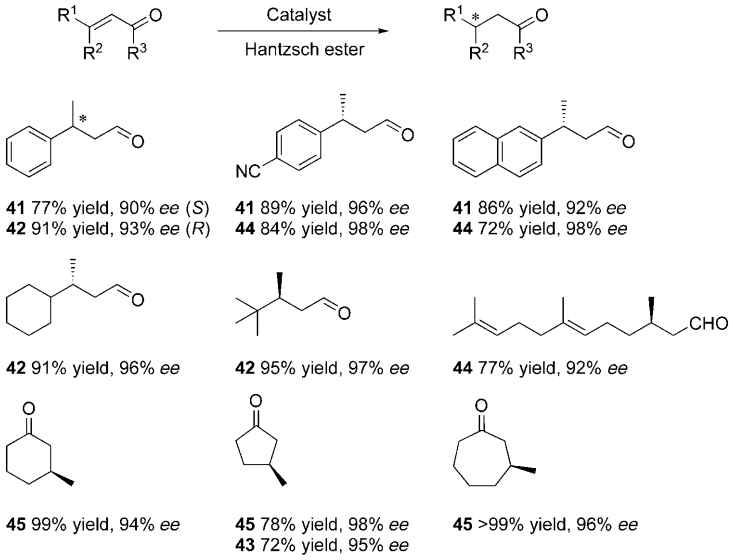
Scheme 18. Organocatalysts for iminium catalysis.



Scheme 17. Iminium and Brønsted acid catalysis in ATH.

could catalyze the selective reduction of the C=C double bond of α,β-unsaturated aldehydes by using Hantzsch ester and its derivatives as the hydrogen donor.[67] Subsequently and almost simultaneously, List and MacMillan reported that the chiral ammonium catalysts **41**[68] and **42**[69] catalyzed the ATH of β-disubstituted α,β-unsaturated aldehydes with high *ee* values, regardless of the geometry of the aldehydes (Scheme 18). Later List and co-workers introduced the concept of asymmetric counteranion-directed catalysis into this reaction by using catalyst **44** (Scheme 18), in which the chirality stems from the counteranion.[70] α,β-Unsaturated ketones are more-challenging substrates; but they could be reduced with catalyst **43**[71] or by using catalyst **45** (Scheme 18) with matched chiral elements.[72] Scheme 19 shows some representative products obtained by organocatalytic ATH through the iminium cycle.

As with chiral ammonium salts, chiral Brønsted acids are also powerful in organocatalytic asymmetric synthesis.[73] The application of chiral Brønsted acid catalysis in ATH was first reported by Rueping and co-workers, who used the chiral phosphoric acid **47** as catalyst in the reduction of ketimines by Hantzsch ester (Scheme 20).[74] Subsequently, a more enantioselective catalyst **48** was disclosed by List and co-workers for the same reduction.[75] MacMillan and co-workers extended the catalysis into asymmetric direct reductive amination (DRA) of ketones with aromatic amines; the chiral phosphoric acid **50** displayed a broad substrate scope and high enantioselectivity.[76] In a related study, List and co-workers showed that DRA of α-substituted aldehydes with the chiral phosphoric acid **49** as catalyst is feasible, through a process of dynamic kinetic resolution (DKR).[77] Recently, the asymmetric reduction of α-iminoesters to produce chiral α-amino esters was achieved by Antilla and co-workers by using catalyst **53**, affording excellent enantioselectivities.[78] The reaction could be performed in a one-pot manner for some substrates without comprising the *ee*



Scheme 19. Reduction products resulting from α,β-unsaturated compounds.

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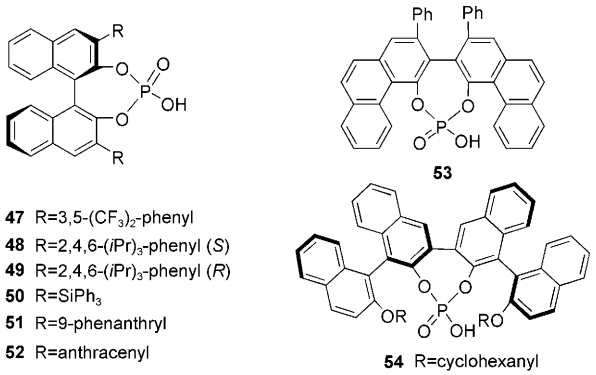
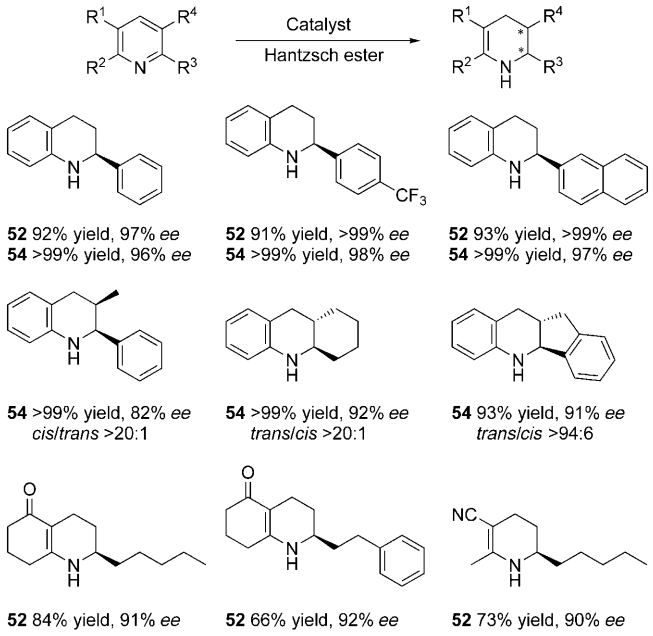


Scheme 20. Organocatalysts based on Brønsted acids.

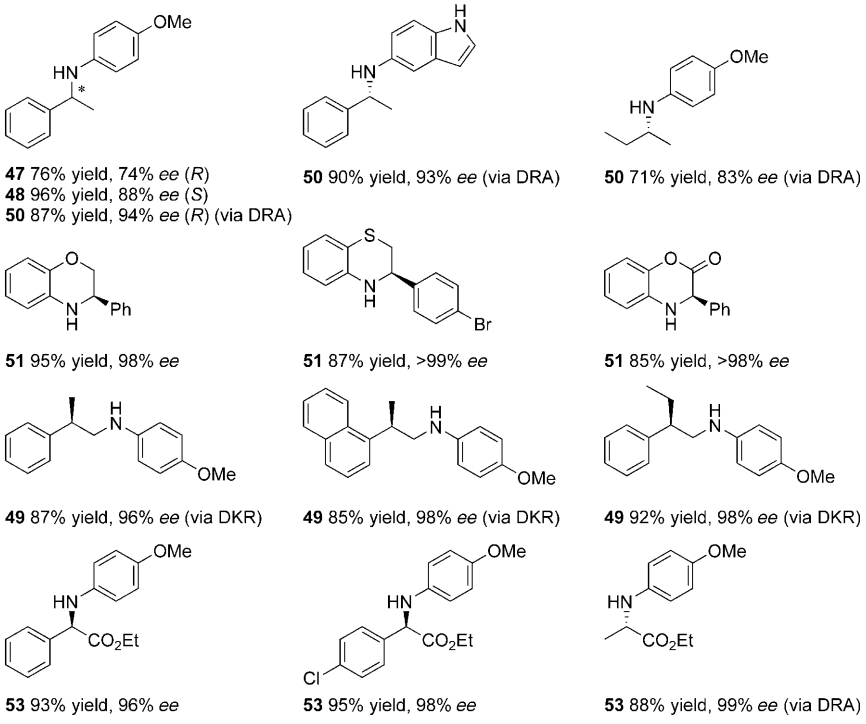
values. Heterocyclic compounds such as benzoxazines, benzothiazines, and benzoxazinones were reduced by using the more sterically congested chiral phosphoric acid **51**, with a catalyst loading as low as 0.01 mol%.[79] Scheme 21 shows some representative products obtained from these reactions with the catalysts **47**–**51** and **53**.

Quinolines and pyridines have also been reduced under organocatalytic ATH conditions. Examples are presented in Scheme 22. The phosphoric acid **52** (Scheme 20) is a good catalyst, affording up to 99% *ee*.[80] Several natural products, including galipinine, cuspareine, and angustureine, were synthesized by quinoline reduction with good yields and *ee* values. Recently Du and co-workers disclosed the use of catalyst **54** (Scheme 20) for the reduction of quinolines, with *ee* values up to 98% obtained; the catalyst loading could be lowered to 0.2 mol%.[81] As is seen in Scheme 22, pyridine compounds are also reducible with the catalyst **52**.[82]



Scheme 22. Reduction of quinolines and pyridines.

The Jacobsen-type thiourea catalyst **55** (Scheme 23)[83] has recently been exploited for the asymmetric reduction of β,β-disubstituted nitroolefins by Hantzsch ester, providing excellent yields and enantioselectivity. An example is seen in Scheme 23.[84] There appears to be no organocatalyst capable of reducing C=O bonds with Hanstzch ester. However, when using a copper oxazoline complex **56** as the catalyst, Hantzsch ester is shown to reduce ketone esters (Scheme 23).[85]



Scheme 21. Amine products resulting from imine reduction, DRA, or DKR of aldehydes with amines.

5. Water as Solvent

While enzymatic-type ATH normally takes place in water, most man-made catalysts use organic media. ATH in water can simplify the operation procedures and, at the same time, make the process more economic and "greener"; significant progress has been recorded in this direction in the past few years.[11f–h,16e,54,57,63,86–89] Reports on ATH in aqueous media were initially concerned with organic/water biphasic systems, with efforts focusing mainly on the design of water-

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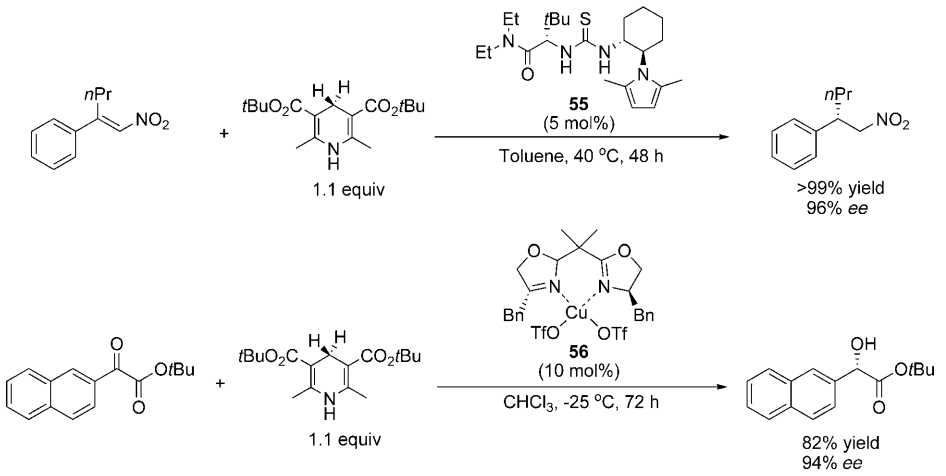
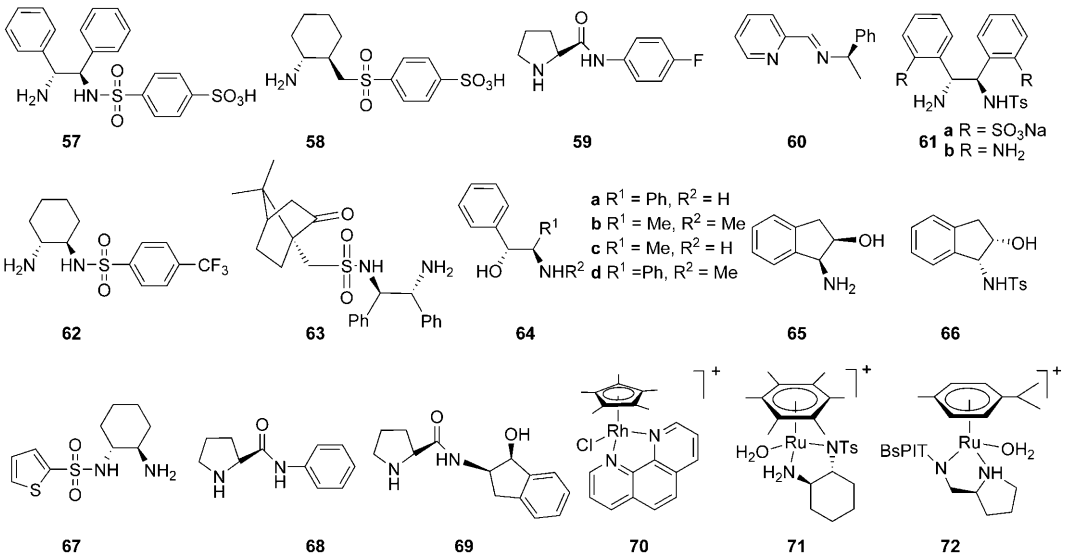


Scheme 23. Reduction of the C=C bond of a nitroolefin and the C=O bond of a ketoester with Hantzsch ester.

soluble catalysts based on the modification of existing ligands.[88a,b,f] However, the resulting catalysts displayed activities and/or enantioselectivities lower than might be expected. In 2004, we found that, without any modification, the Noyori–Ikariya catalyst Ru-**1**, derived in situ from $[RuCl_2(p\text{-cymene})]_2$ and **1** (Scheme 1), enables efficient ATH in neat water.[88g] The reaction was considerably faster than in organic media and afforded excellent enantioselectivities. For example, acetophenone was reduced in 95% *ee* in 1 h at an S/C ratio of 100 at 40 °C.

We soon found that, when combined with $[RuCl_2(p\text{-cymene})]_2$, $[Cp^*RhCl_2]_2$, or $[Cp^*IrCl_2]_2$, other ligands, which were designated for organic solvents, were also effective for ATH in water with no need for modification or organic solvents. A number of ligands/catalysts have since been explored for ATH in water; selected examples are shown in Scheme 24; additional examples are given elsewhere (ligands **1** and **2**, Scheme 1).[16e,63,88,89] It is of further interest that the aqueous-phase ATH has already seen commercial applications.[11g,88r] A recent review summarized the progress made in ATH in water;[11h] hence it will not be repeated here. Instead, for comparison, we summarize in Table 2 the results obtained in the ATH of the benchmark substrate acetophenone with various catalysts. In general, the catalysts were derived from the ligands and metal precursors aforementioned, for example, Ir-**61** from $[Cp^*IrCl_2]_2$ and ligand **61** in water. Briefly, the monotosylated diamines serve as efficient ligands for the ATH of ketones by HCOONa in water. Under the given reaction conditions, the Rh^{III} catalysts led to better performance in terms of reaction rate and enantioselectivity (entries 13, 21, 22, 26, 27, 31, 32, 36, 41, 57–59, 63, and 64, Table 2), and the camphor-sulfonated ligand **63** led to the best enantioselectivity (entries 34–42, Table 2). Often the ATH reactions are run biphasically, as the substrates are usually water insoluble. Being miscible with water, poly(ethylene glycol) (PEG) has recently been used by Fan and coworkers as a cosolvent for aqueous ATH, allowing the reduction to proceed homogeneously (entry 20, Table 2).[89s] It is worth noting that the reduction with Rh^{III} and Ir^{III} catalysts can be performed in the open air without degassing and/or inert gas protection throughout, affording the same conversion and *ee* values (entries 22, 27, and 32, Table 2). However, recent studies from Rauchfuss and Ikariya show



Scheme 24. Examples of ligands/catalysts used for ATH in aqueous media.

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Table 2. ATH of acetophenone with various catalysts in aqueous media.

Entry	Cat.	Solvent	[H][a]	S/C[b]	T [°C]	t [h]	Conv. [%]	*ee* [%]	Ref.
1	Ru-**57**	IPA-H_2O	IPA	200	22	48	96	94	[88a]
2	Rh-**57**	IPA-H_2O	IPA	200	22	24	92	97	[88b]
3	Ir-**57**	IPA-H_2O	IPA	200	22	140	90	82	[88b]
4	Ru-**58**	IPA-H_2O	IPA	200	22	48	91	88	[88a]
5	Rh-**58**	IPA-H_2O	IPA	200	22	18	94	95	[88b]
6	Ir-**58**	IPA-H_2O	IPA	200	22	26	88	96	[88b]
7	Ru-**59**	H_2O	HCOONa	400	40	18	98	69	[88d]
8	Rh-**60**	HCOOH	aq.HCOONa	100	40	24	>99	51	[88e]
9	Ru-**61a**	H_2O	HCOONa	100	40	24	>99	95	[88f]
10	Rh-**61a**	H_2O	HCOONa	100	40	24	92	84	[88f]
11	Ir-**61a**	H_2O	HCOONa	100	40	24	10	58	[88f]
12	Ru-**61b**	H_2O	HCOONa	100	28	0.5	33	95	[89p]
13	Rh-**61b**	H_2O	HCOONa	100	28	0.5	97	97	[89p]
14	Ir-**61b**	H_2O	HCOONa	100	28	0.5	29	94	[89p]
15	Ru-**1**	H_2O	HCOONa	100	40	1	99	95	[88g]
16	Ru-**1**	H_2O	F/T[c]	100	40	1.5	>99	97	[89p]
17	Ru-**1**	H_2O	F/T[c]	1000	40	9	>99	96	[89p]
18	Ru-**1**	H_2O	F/T[c]	5000	40	57	98	96	[89p]
19	Ru-**1**	H_2O	F/T[c]	10000	40	110	98	94	[89p]
20	Ru-**1**[d]	PEG/H_2O	HCOONa	100	40	3	>99	96	[89s]
21	Rh-**1**	H_2O	HCOONa	100	40	0.5	99	97	[89t]
22	Rh-**1**[e]	H_2O	HCOONa	100	40	0.5	99	97	[89t]
23	Ir-**1**	H_2O	HCOONa	100	40	3.5	99	93	[89t]
24	Ir-**1**[e]	H_2O	HCOONa	100	40	12	95	92	[89t]
25	Ru-**2**	H_2O	HCOONa	100	40	2	99	85	[88q]
26	Rh-**2**	H_2O	HCOONa	100	40	0.25	>99	95	[88q]
27	Rh-**2**[e]	H_2O	HCOONa	100	40	0.25	99	96	[88q]
28	Rh-**P2**[f]	H_2O	HCOONa	50	40	10	53	68	[89c]
29	Ir-**2**	H_2O	HCOONa	100	40	3	99	93	[88q]
30	Ru-**62**	H_2O	HCOONa	100	40	2.5	>99	81	[89r]
31	Rh-**62**	H_2O	HCOONa	100	40	0.25	>99	94	[89r]
32	Rh-**62**[e]	H_2O	HCOONa	100	40	0.25	>99	94	[89r]
33	Ir-**62**	H_2O	HCOONa	100	40	1.5	>99	92	[89r]
34	Ru-**63**	H_2O	HCOONa	100	40	2	99	97	[89f]
35	Ru-**63**	H_2O	HCOONa	1000	40	20	95	96	[89f]
36	Rh-**63**	H_2O	HCOONa	100	40	0.7	99	99	[89f]
37	Rh-**63**	H_2O	HCOONa	1000	40	20	89	99	[89f]
38	Ir-**63**	H_2O	HCOONa	100	40	0.7	99	97	[89f]
39	Ir-**63**	H_2O	HCOONa	1000	40	2.5	97	98	[89f]
40	Ru-**63**[d]	H_2O	HCOONa	100	40	2	99	96	[89f]
41	Rh-**63**[d]	H_2O	HCOONa	100	40	0.7	97	98	[89f]
42	Ir-**63**[d]	H_2O	HCOONa	100	40	0.7	99	96	[89f]
43	Ru-**64a**	H_2O	HCOONa	100	40	10	95	50	[89j]
44	Rh-**64a**	H_2O	HCOONa	100	40	20	85	41	[89j]
45	Ir-**64a**	H_2O	HCOONa	100	40	1.5	100	27	[89j]
46	Ru-**64b**	H_2O	HCOONa	100	40	3.5	>99	73	[89j]
47	Rh-**64b**	H_2O	HCOONa	100	40	22	77	68	[89j]
48	Ir-**64b**	H_2O	HCOONa	100	40	2.5	100	54	[89j]
49	Ru-**64c**	H_2O	HCOONa	100	40	5	97	60	[89j]
50	Rh-**64c**	H_2O	HCOONa	100	40	5	63	31	[89j]
51	Ir-**64c**	H_2O	HCOONa	100	40	5	61	7	[89j]
52	Ru-**65**	H_2O	HCOONa	100	40	12	84	71	[89j]
53	Rh-**65**	H_2O	HCOONa	100	40	20	92	55	[89j]
54	Ir-**65**	H_2O	HCOONa	100	40	5	>99	27	[89j]
55	Ru-**65**[d]	H_2O	HCOONa	40	RT	–	81	73	[89u]
56	Ir-**7**	H_2O	HCOONa	100	60	47	99	62	[89e,k]
57	Rh-**67**	H_2O	HCOONa	100	40	0.5	100	93	[89n]
58	Rh-**67**[g]	H_2O	HCOONa	100	40	0.5	100	94	[89n]
59	Rh-**67**[h]	H_2O	HCOONa	100	40	0.5	100	94	[89n]
60	Ru-**66**	H_2O	HCOONa	40	50	–	13	81	[89u]
61	Ru-**68**	H_2O	HCOONa	20	30	12	100	67	[89v]
62	Ru-**69**	H_2O	HCOONa	20	30	40	100	84	[89v]
63	**11**	H_2O	HCOONa	200	28	3	100	96	[16e]
64	**70**	buffer[i]	HCOONa	330	37	24	20	98	[63][63]
65	**71**	H_2O	HCOONa	100	60	2–5	>99	93	[89m]

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Table 2. (Continued)

Entry	Cat.	Solvent	[H][a]	S/C[b]	T [°C]	t [h]	Conv. [%]	*ee* [%]	Ref.
66	**72**[j]	H_2O	HCOONa	100	60	2–5	>99	44	[89m]

[a] [H] refers to hydrogen source. [b] S/C is substrate to catalyst molar ratio. [c] F/T = formic acid/triethylamine (mixtures at various molar ratios). [d] The opposite enantiomer of ligand was used. [e] The reaction was carried out in open air without inert gas protection throughout. [f] **P2** = oxide-supported ligand **2**; the reaction was carried out in air. [g] In the presence of the surfactant CTAB (cetyltrimethylammonium bromide). [h] In the presence of the surfactant SDS. [i] Buffer = phosphate buffer (pH 7); the reaction was carried out in the presence of enzyme (see Scheme 15). [j] BsPIT in Scheme 24 refers to 2-(*S*)-(2,4,6-triisopropyl-benzenesulfonylamino)methylpyrrolidine.

that the intermediate M-H species involved in the ATH can react with O_2.[50]

More recent studies of ATH in aqueous media have also been reported. Although β-amino alcohol ligands have been considered incompatible with HCOOH/Et_3N azeotrope for ATH in the past,[11b,f] the results in Table 2 (entries 43–55, 60) show that these ligands (**64**–**66**, Scheme 24) do catalyze the ATH of acetophenone by formate in water; however, they afforded only moderate reaction rates and enantioselectivities.[88n,89j,u] Using the opposite enantiomer of ligand **65**, the ATH of ketones with Ru^{II} catalyst in water was reported very recently and a similar result was obtained at room temperature at an S/C ratio of 40.[89u] Interestingly, it was shown that *N*-substitution in these ligands, for example, **65** vs **66**, could lead to the inversion of product configuration; but the ATH was observed with low conversions (entries 55 and 60, Table 2).[89u] However, terpene-based chiral amino alcohol ligands afforded no conversion in the Ru^{II}-catalyzed ATH of ketones with formate in water, although they were effective for the same reaction in IPA.[89h] Earlier, L-amino acids were combined with Cr^{II} to catalyze the ATH of ketones and of the C=N bond of oximes in a mixture of DMF/H_2O or formamide solution; good yields and moderate *ee* values were obtained.[90]

New ligands/catalysts have also been explored for ATH in water. The reduction of acetophenone in water with the tethered complex **11** afforded full conversion with 96% *ee* at 28°C in 3 h (entry 63, Table 2), and in the case of 2-acetylfuran, an S/C ratio of 10000 was feasible, with 98% *ee* obtained.[16e] Moreover, this catalyst enables aliphatic ketones to be reduced in water, albeit with slightly lower *ee* values (84% *ee* for ATH of 1-acetylcyclohexane, see Scheme 25). The ATH of α-substituted acetophenones with a catalyst derived from the ligand **7** and $[IrHCl_2(cod)]_2$ displayed better enantioselectivities than that of acetophenone (entry 56, Table 2) as shown by Gao and co-workers; for example, propiophenone was reduced in 88% *ee* at 60°C at an S/C ratio of 100 in the presence of surfactant.[89e,k] The same reduction could also be carried out in open air and at a higher S/C ratio of 8000.

Based on ligand **2**, Somanathan and co-workers recently prepared a series of functionalized cydn (*trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine) ligands which contained pyridine, imidazole, isoxazole, benzoxaizole, and thiophene groups.[89n] The catalyst Rh^{III}-**67** (Scheme 24) afforded the best performance for the ATH of acetophenone in water with or without a surfactant (entries 57–59, Table 2). The proline amide ligands were also examined in the Ru^{II}-catalyzed ATH of ketones in water, furnishing moderate *ee* values (entries 61 and 62, Table 2).[89v]

The water-soluble Ru^{II}-arene complexes **70**–**72** were demonstrated by Süss-Fink and co-workers to be effective for both ketone and imine reduction by HCOONa in water.[89m] In the case of imines, both cyclic and acyclic substrates could be reduced by the catalysts, with *ee* values of up to 91% obtained for acyclic and 88% for cyclic ones. Slightly earlier, Deng and co-workers reported that imines and iminiums could be smoothly reduced by HCOONa with Ru^{II}-**61a** in water with the aid of a surfactant.[89i] Moderate to excellent yields and *ee* values were obtained for both imines and iminiums, although acyclic imines failed to be reduced. Very recently, a new water-soluble, aminated ligand **61b** has been applied to ATH in water for both ketones and imines.[89p] In comparison with the related Ru^{II} and Ir^{III} catalysts, Rh^{III}-**61b** afforded the best performance in the ATH of both ketones and imines in terms of reaction rate and enantioselectivity. For instance, the ATH of acetophenone gave a 97% conversion with 97% *ee* in 0.5 h at 28°C and an S/C ratio of 100 (entries 12–14, Table 2). The catalyst also worked well for cyclic imines, affording up to 93% *ee*. To reflect on the potential scope of the aqueous ATH, selected examples obtained with the catalysts aforementioned are presented in Scheme 25.

Transfer hydrogenation of aldehyde in water has also been demonstrated. The iridium catalyst **38** (Scheme 8) showed excellent catalytic activity and was highly chemoselective to the formyl group, with TOFs of up to $1.3 \times 10^5\ h^{-1}$ being reached in the reduction of benzaldehyde by HCOONa in water.[54a,b] Remarkably, the catalyst and analogues also catalyze the hydrogenation of aldehydes in water.[54b] Earlier, $[Cp_2Mo(H)(OTf)]$ was reported by Kuo and co-workers to catalyze the transfer hydrogenation of ketones and aldehydes in aqueous media.[91]

A significant feature of the aqueous ATH is that the reaction rates vary with the pH value of the solution. We initially demonstrated this in the ATH of acetophenone with Ru^{II}-**1** in water.[88p] It was shown that an increase of 1 pH unit at about pH 3.9 could result in an increase in rate of about 20 times; little reduction occurred at lower pH value, but the pH value increased with time owing to the decomposition of HCOOH into CO_2 and H_2 by the catalyst.[88p] Of note is that the enantioselectivity varied with the pH value as well, at

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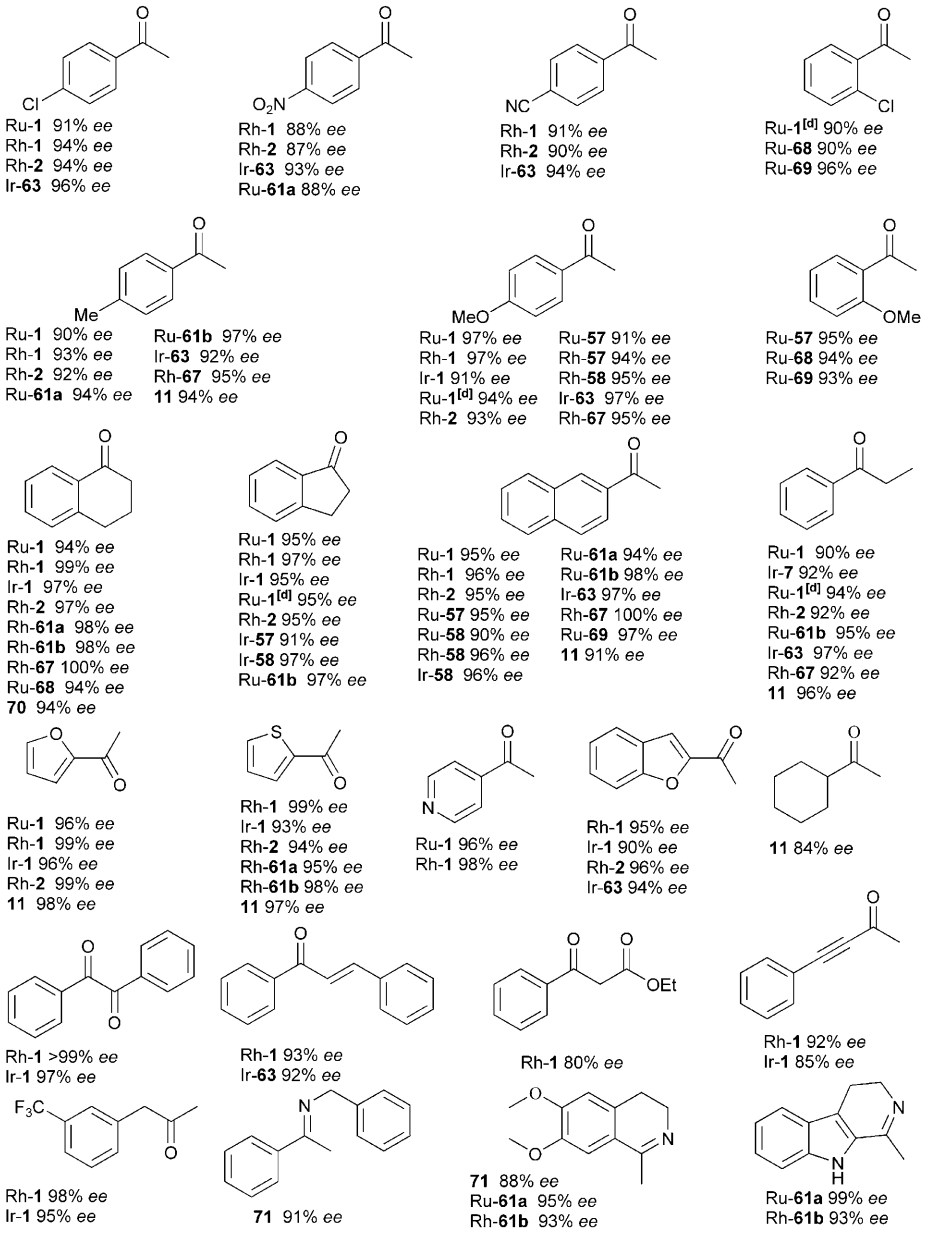

Scheme 25. Selected results for ATH in water ($\geq 90\%$ *ee*). See Table 2 for reaction conditions and references.

low but not high pH values.[11h,88p] Further studies have revealed that this pH dependence is common for the ATH of ketones in water.[11h,51,88k,o,89h,j,m,p,t] For example, the Rh^{III}-**1** and Ir^{III}-**1** catalysts displayed a pH window of 5.5–10 and 6.5–8.5, respectively, for TOF $> 50\ h^{-1}$ in the ATH of acetophenone in water (Figure 1).[89t]

The mechanism of aqueous ATH has recently been investigated.[51,88k,89m,p,t] In a study using NMR spectroscopy, kinetic and isotope measurements, and DFT calculations, we showed that the catalytic cycle presented in Scheme 26 is likely to operate in the ATH of ketones in water around neutral conditions.[51] Using the ATH of acetophenone by formate with Ru-**1** as a model reaction, we demonstrated that the Ru^{II}-H and the 16e species are active catalysts in ATH in water, and while the Ru^{II}-H species is visible in the NMR spectra, the formato complex could not be detected in either stoichiometric or catalytic reactions. Furthermore, the kinetic profiles of the precatalyst, the Ru^{II}-H, and the 16e species showed no significant difference, indicating that the latter two are involved in the aqueous-phase ATH. Kinetic studies revealed that the rate of the ATH reaction was first order in both the catalyst and ketone substrate, and was inhibited by CO_2. Together with the NMR measurements, this suggests that the ATH rate is limited by hydrogen transfer from ruthenium to the ketone, having a transition state resembling that proposed by Noyori for non-aqueous media (Scheme 26).[9c,d]

Water has been demonstrated to accelerate the ATH. For instance, in the stoichiometric reduction of acetophenone by the isolated Ru^{II}-H species, the rate in wet CD_2Cl_2 was 6 times that in dry CD_2Cl_2. Further insight was gained in DFT calculations, which showed that water participates in the transition state of hydrogen transfer, stabilizing it by about 4 kcal mol^{-1} through hydrogen bonding with the ketone oxygen atom. Of further interest is that the calculations suggest that the participation of water renders the hydrogen transfer more stepwise rather than con-

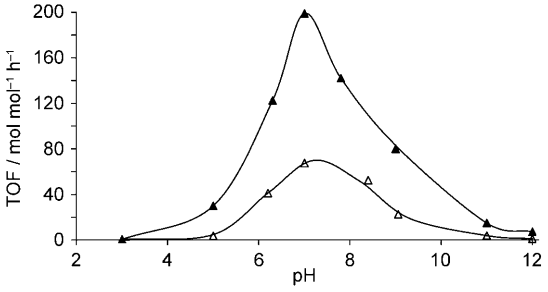

Figure 1. Initial TOF vs. pH values for the ATH of acetophenone with M-**1** (M = Rh: -▲-; M = Ir: -Δ-) in water at 40 °C.

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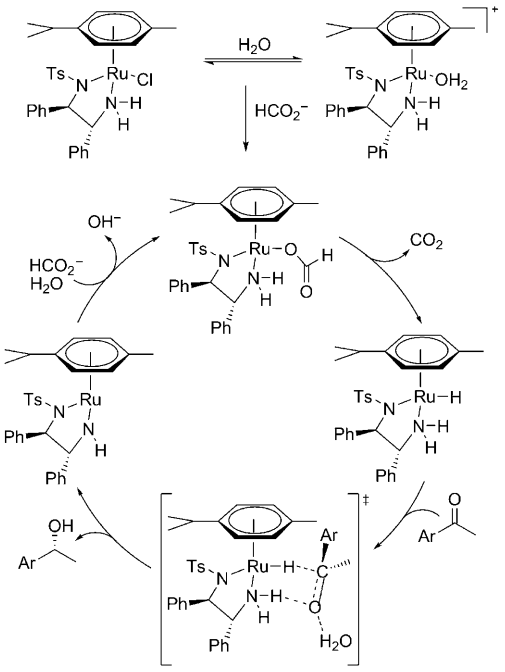
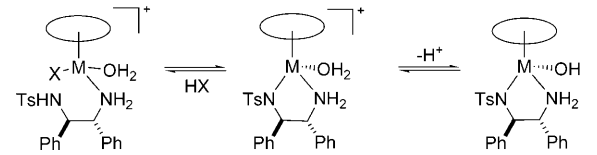


Scheme 26. Proposed mechanism for the ATH of ketones in water.

certed.[51] This is in line with kinetic isotope measurements. A similar solvent effect has recently been reported in a DFT study on a model reduction of formaldehyde in methanol.[92]

The NMR studies shed light on the effect of pH value on the ATH. The precatalyst and the Ru^{II}-H species were shown to be protonated at the amido nitrogen atom of their tsdpen ligand under acidic conditions, leading to ring-opening of the chelating ligand. Under neutral conditions, water coordinates to the 16e species, presumably forming a Ru^{II}-OH species. Thus, apart from the equilibrium effect of pH



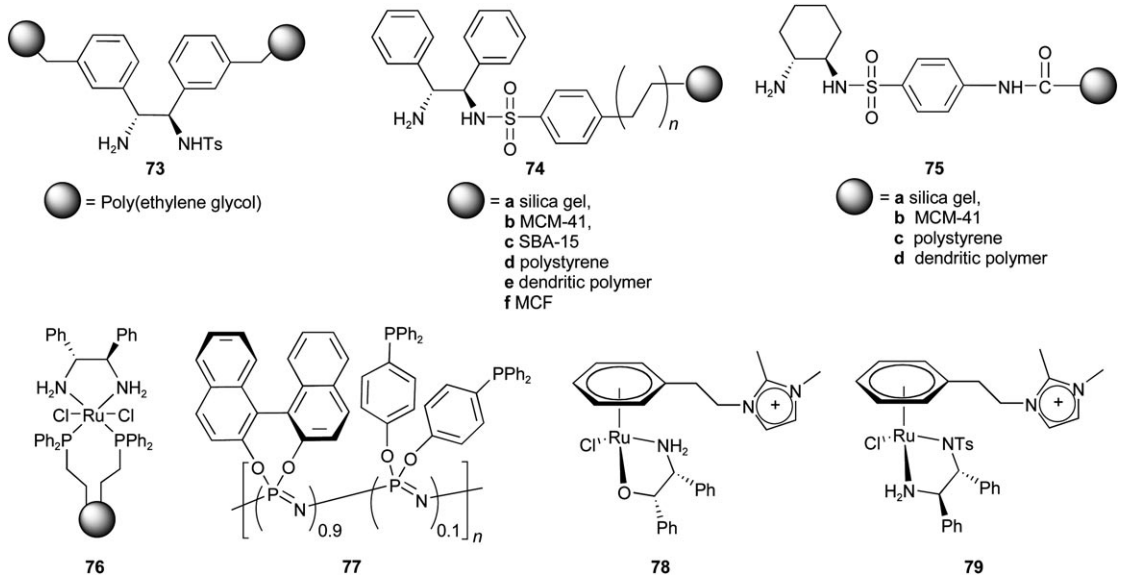
Scheme 27. Formation of inactive M-OH species and less effective, ring-opened species from the active catalyst as a result of pH variation.

on [$HCOO^-$] (pK_a 3.6), the pH effect on both the reaction rate (Figure 1) and enantioselectivity aforementioned may be accounted for by invoking the equilibrium suggested in Scheme 27.

6. Immobilized Catalysts for Easy Separation and Reuse

As with most other homogeneous catalysts, chiral M-diamine catalysts explored in ATH are usually expensive and cannot be easily separated from the products. From a practical, economical, and environmental viewpoint, heterogeneous catalysis is usually preferred over homogeneous catalysis.[87d,93] In response to this, immobilized ATH catalysts have been developed recently. Selected examples are shown in Scheme 28. These ligands/catalysts (**73**–**79**) have been applied in both organic and aqueous media for the ATH of ketones, affording good to excellent results in terms of activity, enantioselectivity, and recyclability (Table 3).

The water-soluble, PEG-immobilized ligand **73** represents one of the most efficient ligands for ATH in water.[88h] A wide range of aromatic ketones can be reduced by Ru^{II}-**73** in water using HCOONa as the hydrogen source, with the results comparable to those obtained with Ru-**1** under the same conditions. Importantly, the catalyst could be reused



Scheme 28. Immobilized ligands/catalysts for ATH.

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Table 3. Comparison of supported catalysts for ATH of acetophenone.

Entry	Cat.	Solvent[a]	[H]	Runs	t [h]	Conv.[%]	*ee* [%]	Ref.
1	Ru-**73**	F/T	HCOOH	3	20	99–56	91–82	[94]
2	Ru-**73**	H_2O	HCOONa	14	1–48	99–87	93	[88h]
3	Ru-**74a**	F/T	HCOOH	5	6–44	>99–94	97	[88m]
4	Ru-**74a**	H_2O	HCOONa	7	2–60	>99–60	96	[88m]
5	Ru-**74b**	F/T	HCOOH	3	8–88	99–44	96	[88m]
6	Ru-**74b**	H_2O	HCOONa	1	22	>99	87	[88m]
7	Ru-**74c**	F/T	HCOOH	4	8–72	>99–45	97–96	[88m]
8	Ru-**74c**	H_2O	HCOONa	4	8–47	>99–43	92–94	[88m]
9	Ru-**74d**	H_2O	HCOONa	5	3[b]	100	98–97	[89a,o]
10	Rh-**74d**	H_2O	HCOONa	1	10	99	98	[89a,o]
11	Ru-**74e**	DCM	F/T	6	20–40	98–52	97–87	[95]
12	Ru-**74f**	DCM	F/T	6	–	100–94	98–97	[96]
13	Rh-**75d**	H_2O	HCOONa	6	0.7–1.5	>99–85	96–94	[89d]
14	**76**	DCM	IPA	8	24–48	>99	>99–94	[97]

[a] F/T refers to formic acid/triethylamine azeotrope. [b] The reaction time for the recycling runs was not given.

over 14 runs without loss of enantioselectivity in the ATH of acetophenone in water, thus exhibiting excellent recyclability and lifetime (entry 2, Table 3).[88h] In contrast, when carried out in HCOOH/Et_3N azeotrope without water, the catalyst could only be reused two times without the rates and *ee* values being eroded (entry 1, Table 3).[94] The use of other types of supported ligands has also been demonstrated (**74**–**76**, Scheme 28).[88i,m,89a,d,o,95–97] In particular, the group of Deng has designed a series of solid-supported diamine ligands (**74** and **75**, Scheme 28) and water-soluble ligands (**61**, Scheme 24 and Table 2). In most cases, these ligands afforded good to excellent *ee* values and could be recycled up to 11 times (entries 12–14, Table 2; entries 3–13, Table 3). Mesoporous materials functionalized with cydn (**75b**) has recently been reported to allow for the Rh^{III}-catalyzed ATH of ketones in water.[89c] A silica-supported Ru^{II}-dpen catalyst **76**, reminiscent of the Noyori Ru^{II}-diphosphine-diamine hydrogenation catalyst, exhibited surprisingly high catalytic activity (>99% yields for all tested ketones) and excellent enantioselectivities (>98% *ee*) in the ATH of various aromatic ketones.[97] The catalyst can be recycled up to eight times (entry 14, Table 3). Polymeric phosphines (**77**) and pyridines have also been used in achiral transfer hydrogenations of ketones with good reusability.[98]

Interestingly, ionic liquids have been explored as immobilizing media for ATH.[99] A good example is seen in the catalysts **78** and **79**, which have been applied to the ATH of ketones in the ionic liquid [bdim][PF_6] (bdim = 1-butyl-2,3-dimethylimidazolium) with HCOOH/Et_3N azeotrope as the hydrogen source. Excellent *ee* values and moderate rates were obtained, and the catalyst could be recycled up to five times.[99a]

7. State of the Art, and Quo Vadis?

A number of powerful ATH catalysts have appeared in the last few years, with activities and enantioselectivities approaching or surpassing some of the best AH catalysts. Most of them are embedded with a metal–ligand bifunctionality, but not all, and this is important as it may point to overlooked reaction pathways. Although ruthenium, rhodium, and iridium still dominate the scene, "greener" and inexpensive iron catalysts are on the horizon. "Greening" ATH is also made possible by employing water as solvent and immobilizing soluble catalysts. Traditionally, ATH derives hydrogen from alcohols and formate salts but not from H_2; however, "universal" catalysts are emerging, blurring the boundary of ATH and AH. Most often, ATH catalysts are explored for the reduction of C=X (X = O, N, C) bonds; however, they have also shown utility in reducing NAD^+ and analogues, supplying the hydrogen source to enzymatic and organocatalysis.

Throughout the survey, it is evident that C=O double-bond reduction is the most extensively studied and successful with transition-metal-catalyzed ATH. The Noyori-type bifunctional catalysts are generally good for aromatic ketones,[7a,b,13b,d,16a] but not for aliphatic ones, probably because of the lack of C–H–π interactions that are crucial for the stereocontrol.[100] Efforts are being made to tackle the low enantioselectivity of aliphatic ketones. The introduction of a tether into the Noyori catalysts could improve the enantioselectivity for aliphatic ketones in some cases,[16c] and the Ru^{II}-oxazoline complex **33** provided excellent enantioselectivity for aromatic ketones and some aliphatic ketones.[45d] Of particular note is the Ru^{II} complex bearing the phosphite ligand **15**, which provides satisfactory enantioselectivity for a range of aliphatic ketones, as does the β-cyclodextrin-modified Ru^{II} catalyst shown in Scheme 13.[19,58,59]

The reduction of C=C bonds by ATH is less studied. There are a few early reports using Ru^{II}-binap complexes in the reduction of conjugated acids, affording about 90% *ee*,[39,40] and some highly polarized C=C double bonds are reduced using the Ru^{II} catalyst.[101] Generally, however, carbonyl groups are reduced preferentially under transition-metal-catalyzed ATH conditions. In contrast, in organocatalysis the amine-catalyzed reduction of α,β-unsaturated aldehydes or ketones by Hantzsch ester led only to the saturation of the C=C double bonds.[67–69,71,72]

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The ATH of imines has attracted much attention recently. However, few ligands/catalysts can offer good to excellent results for the ATH of C=N double bonds up to now. Cyclic imines could be reduced with high *ee* values using the M-tsdpen-type catalysts.[8a,89i,m,p,102] The reduction could even be carried out in water with water-soluble catalysts[89i,m,p] or by using supported catalysts.[96] In related studies, α-branched cycloketimines have been resolved through a dynamic kinetic process, affording up to 99:1 diastereoselectivity and 98% *ee*.[103] Acyclic imines seem to be more challenging with transition-metal catalysis; good enantioselectivities were obtained only for some special substrates.[89m,104] The Brønsted acid catalysis using Hantzsch ester as the hydrogen source provides a complementary route. Generally acyclic imines are good substrates under organocatalytic ATH conditions; up to 93% *ee* for ketimines was achieved.[74,75] Various heterocyclic compounds including benzoxazines, benzothiazines, benzoxazinones, quinolines, and pyridine derivatives could be reduced with high enantioselectivities.[79,80,82]

Most acyclic ketimines are difficult to synthesize, which makes DRA of ketones attractive. The challenge in DRA is to find a catalytic system which reduces the C=N bond preferentially over its C=O counterpart. There are only two successful transition-metal-catalyzed examples of DRA by ATH. Kadyrov and co-workers found that [$RuCl_2$((*R*)-tolbinap)] catalyzed the DRA of ketones with ammonium formate as both the hydrogen and amine source, affording up to 95% *ee*.[105] An intramolecular DRA was disclosed by Wills and co-workers adopting Noyori's transfer hydrogenation system.[106] In organocatalysis, the DRA of ketones and amines[76] and the DKR of α-branched aldehydes have been successfully demonstrated, as discussed above.[77]

8. Conclusion

In concluding this Focus Review, it is clear that the past decade or so has witnessed great strides in developing catalysts for ATH reactions. This is largely triggered by the seminal discovery made by Noyori and co-workers in 1995. Time will attest that with the ongoing endeavors and new insights, ATH will become a more versatile tool, enabling hydrogenations that are tractable or intractable with H_2 while offering unique insights into the chemistry of hydrogen transfer in laboratories and in nature.

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